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Risk Factors for Intravesical Recurrence Following Urothelial Carcinoma of the Upper Urinary Tract: No Relationship to the Mode of Surgery

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Objective: The aim of this study was to clarify whether intravesical recurrence of upper urinary tract cancer after treatment is related to the mode of surgery or other oncological factors.
Methods: We evaluated 106 patients (mean age 70.4 years; mean follow-up 24.0 months) who underwent surgery for the upper urinary tract cancer at Hiroshima University and its affiliated hospitals between January 1995 and August 2005. Seventy-nine of the patients underwent retroperitoneoscopy-assisted radical nephroureterectomy (RN) and 27 underwent nephroureterectomy by open surgery (OS). Fifty-two patients had renal pelvic tumors, 48 had ureteral tumors, and six had both renal pelvic and ureteral tumors. Twenty-eight (26%) of the 106 patients had a pre-operative history of bladder cancer. We identified the risk factors predicting intravesical recurrence of upper urinary tract cancer according to the type of previous surgery using the Kaplan–Meier method, log-rank test, and univariate and multivariate analysis using the Cox proportional hazards model.
Results: Thirty-one (29%) of the 106 patients developed bladder tumors post-operatively. The 2-year intravesical recurrence-free rate was 55% in the RN group and 60% in the OS group. There was no significant difference ($P = 0.51$, log-rank test) in the rate of intravesical recurrence between the two groups. Multivariate analysis identified only a history of pre-operative bladder tumor (HR = 3.25, $P = 0.003$) as a predictor of post-operative intravesical recurrence.
Conclusions: Intravesical recurrence after surgery for upper urinary tract cancer is not related to the mode of surgery (i.e. laparoscopy-assisted or open surgery) employed. The only risk factor for intravesical recurrence is a history of bladder cancer.

Key words: laparoscopy – intravesical recurrence

OBJECTIVE

Radical nephroureterectomy with open excision of the distal ureter with a bladder cuff is considered to be the gold standard for the treatment of transitional cell cancer (TCC) of the upper urinary tract (1). However, this procedure requires either two skin incisions or an extended flank incision, both of which are associated with significant post-operative morbidity.

In 1991, Clayman first described the technique of laparoscopy-assisted nephroureterectomy (2), which was soon adopted by various urologists worldwide (3,4). However, the aggressive nature of upper tract TCC and the high risk of recurrence have caused many to be reluctant to treat this disease laparoscopically. With increasing acceptance of laparoscopic radical nephrectomy for renal cancer, however, laparoscopic nephroureterectomy has gained wide acceptance in the management of upper tract TCC. Additionally, some authors have tried to compare their data with the results of contemporary series of patients treated by open nephroureterectomy (5–7).

In this study we attempted to clarify whether intravesical recurrence after treatment of upper urinary tract TCC is related to the type of previous surgery (i.e. laparoscopy or open surgery) and other oncological factors.

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PATIENTS AND METHODS

We evaluated 106 patients who underwent surgery for upper urinary tract TCC at Hiroshima University and its affiliated hospitals between January 1995 and August 2005. Seventy-nine of the patients underwent retroperitoneoscopy-assisted radical nephroureterectomy (RN group) and 27 underwent nephroureterectomy by open surgery (OS group). The primary lesion was located in the renal pelvis in 52 patients, in the ureter in 48, and in both the renal pelvis and ureter in six patients. Of these 106 patients, 100 (94.3%) had transitional cell carcinoma, five (4.7%) had transitional cell carcinoma with squamous cell carcinoma, and two (1.9%) had transitional cell carcinoma and adenocarcinoma. The pathological stage and grade were classified according to the International Union Against Cancer, tumor, metastasis, node (UICC-TMN) classification system (8) as modified by the Joint Committee of the Japan Urological, Pathological Society (9). Twenty (25%) patients in the RN group and eight (30%) patients in the OS group had a pre-operative history of transurethral resection for superficial bladder cancer. Ten (13%) patients in the RN group received adjuvant chemotherapy, which consisted mainly of systemic chemotherapy with methotrexate, cisplatin, terarubicin and vinblastine (M-VEC) in nine, and intravesical infusion of pirarubicin hydrochloride (THP) in one. Four (15%) of the patients in the OS group received adjuvant chemotherapy with M-VEC. The median follow-up time was 17.5 months (range 1–97 months). Routine follow-up consisted of physical examination, cystoscopy and urine cytologic examination every 3 months during the first 2 years, and every 6–12 months thereafter. Chest radiography, and chest and abdominal computed tomography, excretory urography and abdominal ultrasonography were performed annually, depending on the clinical stage of the cancer in the upper urinary tract.

We separated urothelial cancer in the upper urinary tract into four categories according to the location of the disease: renal pelvis, and upper, mid and lower ureter. An upper ureteral lesion was defined as a site corresponding to the level of the ureteropelvic junction down to the iliac crest, a mid ureter lesion as one down to the lower rim of the sacrum, and a lower ureter lesion as one down to the ureteral orifice. If cancers were found in two or more different sites in the upper urinary tract, we considered the lowest site as the cancer location.

Surgical Procedure

Retroperitoneoscopy-assisted Radical Nephroureterectomy (RN)

The surgical procedures were performed as described previously by Mita et al. (10). In brief, three ports were placed in the retroperitoneal space with the patients in the kidney position. After the quadratus lumborum fascia had been identified, the lateroconal fascia and the posterior renal fascia were opened longitudinally. Blunt dissection was performed between the layers covering the perirenal fat and the renal fascia upwards and medially to identify the renal artery and vein located at the renal hilum. First the renal artery was dissected, followed by the renal vein. The medial layer of the posterior fascia was dissected from the anterior portion around the perirenal fat. The upper pole and medial aspect of the renal fascia were dissected from the fat tissue including the adrenal gland in case non-adrenalectomy was planned. Then the operation table was rotated to the semiflank position and a 7–10 cm oblique iliac incision was made followed by open distal ureterectomy with excision of a bladder cuff. The specimen was removed *en bloc* from the lower pararectal incision.

Open Surgery (OS)

Under general anesthesia, the patient was placed in the kidney position and the retroperitoneum was accessed through an oblique incision. The retroperitoneal space was developed, and then the renal artery and vein were ligated and transected. The kidneys with Gerota's fascia were freed *en bloc* while preserving the adrenal glands. If the tumors were located in the renal pelvis or upper segment of the ureter, the distal ureters were clipped. The patient was then placed supine and a lower abdominal median incision was made from the pubis to the umbilicus followed by distal ureterectomy with excision of a bladder cuff. The specimen was removed en bloc from the lower abdominal median incision.

Regional lymphadenectomy was not performed in any of the patients in either group.

Statistical Analysis

Comparison of parameters (patient sex and age, side of upper urinary cancer, location of the cancers, prior bladder cancers, pathological grade, clinical stage) between the two groups was carried out using the Mann–Whitney U test and χ^2 test. Identification of the risk factors predicting intravesical recurrence of upper urinary tract cancer was carried out using the Kaplan–Meier method, log-rank test, and univariate and multivariate analysis using the Cox proportional hazards model. For all statistical tests, differences at $P < 0.05$ were considered to indicate a significant difference.

RESULTS

Patient Characteristics

Table 1 shows the data for the RN and OS groups. There were no significant inter-group differences in patient sex, age, side of upper urinary cancer, location of the cancers, prior bladder cancers, pathological grade, or clinical stage. Table 2 shows the characteristic of the prior bladder cancer

of both groups. There were no significant inter-group differences in number of tumor, primary or recurrence, pathological T stage, pathological grade, presence or absence of concomitant CIS.

Operative Data and Oncological Follow-up

A comparison of the operative data and oncological follow-up between the two groups is shown in Table 3. In the RN group, the mean operation time was significantly shorter than in the OS group ($P = 0.007$). Mean follow-up was 16.4 months in the RN group, which was significantly shorter than in the OS group ($P < 0.0001$). It was thought that because we have applied the laparoscopic procedure more recently than open procedure. Adjuvant chemotherapy was performed in high-risk patients with a relatively good performance status. We used two or three cycles of M-VEC chemotherapy in 13 patients and intravesical infusion of THP in one patient. Intravesical recurrence was identified in 22 (28%) of the patients in the RN group and in 9 (33%) of the patients in the OS group (difference not significant). The 2-year intravesical recurrence-free rate was 55% in the RN group and 60% in the OS group (difference not significant). Figure 1 shows the intravesical recurrence-free rate in relation to several oncological parameters. There were no significant differences with regard to pathological T stage, pathological grade, location of cancers and adjuvant chemotherapy. Figure 2 shows the intravesical recurrence-free rate in relation to the method of previous surgery and prior bladder cancer. There was no significant difference in relation to method of previous surgery, but the intravesical recurrence-free rate in patients with prior bladder cancers was significantly lower than that in patients without prior bladder cancers ($P = 0.0002$). We performed univariate and multivariate analysis using the Cox proportional hazards model. In univariate analysis, patient sex and age, side of upper urinary cancer, pathological grade and pathological stage were not the risk factor for intravesical recurrence, but the prior bladder cancer was the risk factor for intravesical recurrence ($P = 0.0002$, HR = 6.51). In multivariate analysis also, prior bladder cancer was the only risk factor for intravesical recurrence ($P = 0.003$, HR = 3.25). Table 4 shows

Table 1. Patient characteristics

	RN ($n = 79$)	OS ($n = 27$)	P value
Male/female	62/17	18/4	0.94
Age	71.4 ± 8.2	67.4 ± 11.3	0.052
Right/left	34/45	7/20	0.12
Tumor location			
renal pelvis	37	15	0.59
ureter	38	10	
renal pelvis + ureter	4	2	
Prior bladder cancer			
yes	20	8	0.66
no	59	19	
Pathological grade			
G1	10	3	0.43
G2	33	16	
G3	36	8	
Pathological stage			
pTis	2	0	0.51
pTa	15	8	
pT1	20	6	
pT2	11	6	
pT3	28	7	
pT4	3	0	

RN, radical nephroureterectomy; OS, open surgery.

Table 2. Characteristics of prior bladder cancer

	RN ($n = 20$)	OS ($n = 8$)	P value
Single/multiple	16/4	6/2	0.84
Primary/recurrence	18/2	7/1	0.79
Pathological grade			
G1	3	1	
G2	9	4	0.65
G3	8	3	
Pathological stage			
pTa	12	6	
pT1	6	2	
pT2	1	0	0.77
pT3	1	0	
Comcomitant CIS			
yes/no	18/2	8/0	–

Table 3. Operative data and oncological follow-up

	RN ($n = 79$)	OS ($n = 27$)	P value
Mean operative time (min)	299.2	350.0	0.007
(range)	(140–637)	(215–610)	
Mean follow-up (months)	16.4	46.2	<0.0001
(range)	(1–57.5)	(1–97)	
Adjuvant chemotherapy			
yes	10	4	0.84
no	69	23	
Intravesical recurrence			
yes	**22**	9	0.59
no	**57**	18	
The 2-year intravesical recurrence-free rate	**55%**	60%	0.51

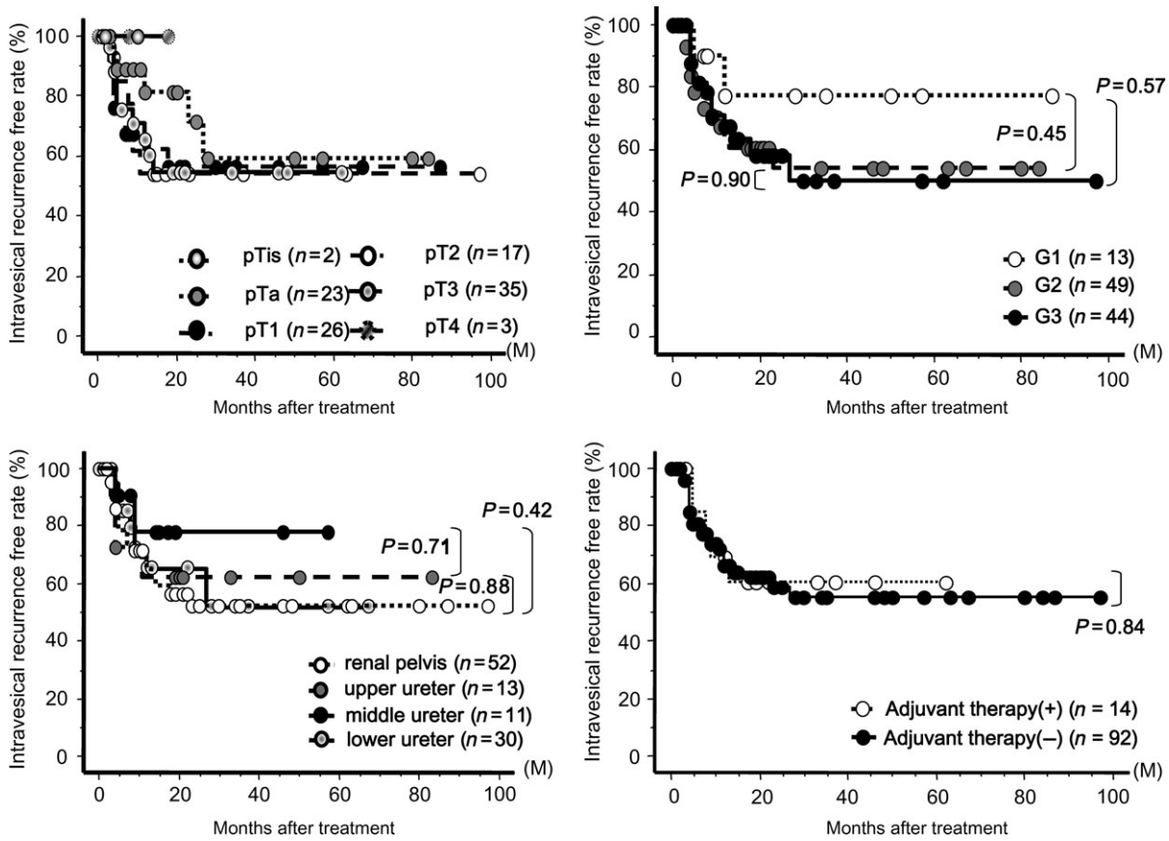

Figure 1. Intravesical recurrence-free rate according to pathological T stage, pathological grade, location of cancers and adjuvant chemotherapy.

the results of multivariate analysis using the Cox proportional hazards model.

DISCUSSION

In this study using multivariate analysis, we clarified that a history of bladder cancer was the only risk factor for intravesical recurrence of upper urinary tract TCC, and that such recurrence was not related to the previous type of surgery.

The advantages of laparoscopic nephrectomy for benign disease have been well proven in several comparative studies revealing a significant reduction of postoperative morbidity (11). However, from an oncological viewpoint, such advantages have to be balanced against possible risk factors such as distant metastasis, port site metastasis, local recurrence and intravesical recurrence.

Several risk factors for the development of distant metastasis have been proposed and can be used to predict the prognosis of patients with urotherial cancer in the upper urinary tract. However, the risk factors for intravesical recurrence have not been fully elucidated. Therefore, identifying these factors after surgery for urotherial cancer in the upper urinary tract would contribute to better management of the disease.

Table 5 shows previous reports of comparisons of clinical outcome between laparoscopic surgery and open surgery for upper urinary tract transitional carcinoma (6,7,12–14). In our study, intravesical recurrence occurred in 28% of patients in the RN group and in 33% of patients in the OS group, consistent with the results of previous studies. No previous report has revealed a significant difference in intravesical recurrence according to the method of upper urinary tract surgery. Saika et al. (15) demonstrated that the intravesical recurrence rate was significantly higher in an endoscopy-assisted group than in a standard open surgery group. However, in their study, the lower ureter was removed by the transurethral stripping method in the endoscopy-assisted group. With this method it is necessary to consider the possibility that cancer cells inside the distal ureteral duct might be seeded into the bladder during the procedure of pulling it inside out.

Togashi et al. (16) reported a high risk of intravesical recurrence in patients with lower ureteral cancer. It seems possible that cancer cells could become implanted on the bladder wall. In our study, however, there was no significant difference according to tumor location.

Many previous studies (17) have demonstrated no correlation between the intravesical recurrence rate and degree of malignancy (i.e. clinical stage and pathological grade), similar to our results. However, it is to be borne in mind that patients with a poor prognosis will die of cancer in the upper urinary tract before developing intravesical recurrence.

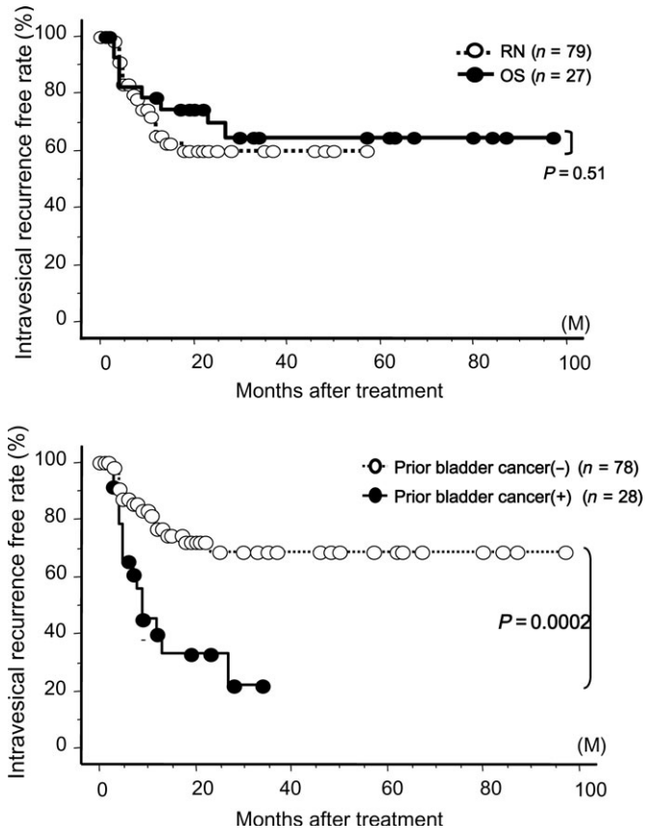

Figure 2. Intravesical recurrence-free rate according to mode of surgery and prior bladder cancer.

Sakamoto et al. (18) reported that 35.8% of patients developed intravesical recurrence, mostly within 2 years after treatment for the disease in the upper urinary tract. In our study, all cases of intravesical recurrence developed within 2 years after surgery. They also demonstrated that multiple-site cancer influenced the subsequent development of cancer in the bladder. This might be related to the multicentric nature of TCC. In relation to the multicentricity of TCC, Kakizoe et al. (19) reported a higher intravesical recurrence rate in patients with both renal pelvic and ureteral cancer than in patients with renal pelvic cancer or ureteral cancer alone. In this study, we could not investigate fully the relationship between intravesical recurrence rate and the number of cancers in the upper urinary tract. However, as prior bladder cancer was the only risk factor for the intravesical recurrence, we speculate that intravesical recurrence may reflect the multicentric character of TCC.

Many previous reports (20) have indicated that associated bladder cancer was not a poor prognostic factor in patients with urotherial cancer in the upper urinary tract. Therefore, treatment for patients who subsequently develop recurrent cancer in the bladder should be individualized, depending on their clinical and pathologic features.

Table 4. Multivariate analysis of factors affecting the intravesical recurrence of urothelial cancer of upper urinary tract using the Cox proportional hazards model

	Hazards ratio	*P* value
Sex: Male/Female	1.18	0.77
Side: Left/Right	0.77	0.52
Age	1.04	0.88
pT state	0.80	0.75
Grade	1.48	0.21
Operation time	1.00	0.38
Adjuvant chemotherapy:		
yes/no	1.02	0.97
Mode of operation:		
RN/OS	1.27	0.59
Prior bladder cancer:		
yes/no	3.25	0.003

Table 5. Oncolological outcome of retroperitoneoscopic versus open total nephroureterectomy

Authors	*N*	Intravesical recurrence (%)	Overall survival	
			2 years (%)	5 years (%)
McNeil (12)	LN	25	7 (28)	74
	OS	42	18 (43)	68
Rassweiler (13)	RN	23	8 (34)	89
	OS	21	3 (14)	83
Shalhav (14)	LN	13	3 (23)	77
	OS	13	7 (54)	69
Klinger (6)	RN/LN	19	2 (11)	95
	OS	15	2 (13)	94
Hattori (7)	RN	65	14 (22)	–
	OS	44	20 (45)	–
Present series	LN	79	22 (28)	–
	OS	27	9 (33)	–

LN, laparoscopic nephroureterectomy.

CONCLUSION

This study has demonstrated that a history of bladder cancer is the only risk factor for intravesical recurrence of upper urinary tract cancer. Retroperitoneoscopy-assisted nephroureterectomy is not inferior to open surgery in terms of the risk of intravesical recurrence. On the contrary, this procedure has advantages over an open approach in terms of post-operative morbidity. Therefore, in the future, laparoscopic surgery will become accepted as a standard treatment, although long-term follow-up studies will be necessary.

Conflict of interest statement
None declared.

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